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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 35/78, 33/00	A2	(11) International Publication Number: WO 94/11010 (43) International Publication Date: 26 May 1994 (26.05.94)
(21) International Application Number: PCT/US93/10670 (22) International Filing Date: 4 November 1993 (04.11.93) (30) Priority data: 07/973,071 6 November 1992 (06.11.92) US (71) Applicant: H.E. STANLEY PHARMACEUTICALS, INC. [US/US]; 101 Orange-Co Circle N.E., Winter Haven, FL 33881 (US). (72) Inventors: HON, David, N., S. ; 103 Charissa Drive, Clemson, SC 29631 (US). STANLEY, R., Thomas ; 123 Lakeview Drive, Auburndale, FL 33823 (US). (74) Agents: LARSON, Marina, T. et al.; Oppedahl & Larson, 1992 Commerce Street, Suite 309, Yorktown Heights, NY 10598-4412 (US).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: COMPOSITIONS OF OAK BARK EXTRACT, RELATED SYNTHETIC COMPOSITIONS, AND METHOD OF USING SAME (57) Abstract Higher concentrations of oak bark ash extract, i.e., greater than 20 % by weight, are useful for the treatment of skin cancers. Lower concentrations of oak bark extract possess additional therapeutic properties not heretofore recognized. For example, preparations containing 40-80 % oak bark extract are useful in the treatment of acute cancerous skin ulcers. In addition, synthetic mixtures containing potassium ions, zinc ions, calcium ions provide many of the same advantageous properties of oak bark extract. The inclusion of rubidium ions and sulfur is also advantageous for some applications.		

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Description

Compositions of Oak Bark Extract, Related Synthetic Compositions, and Method of Using Same

Background of the Invention

This application relates to compositions of aqueous oak bark extract, to synthetic compositions containing the key active ingredients of oak bark extract and to the use of such compositions in the treatment of skin cancer and other skin disorders.

Oak bark extract has been described in United States Patent No. 5,080,900 which is incorporated herein by reference, for use in the treatment of skin ulcers, particularly decubitus ulcers or bed sores. This material in a base of Whitfield's ointment has also been sold under the trade name Bancelok® for use in the treatment of minor skin irritations. The amount of oak bark extract in these materials was relatively low, however. For example, the Bancelok® preparations have continued from 0.25 to 3% by weight of ash-derived components based upon the total weight of the preparation.

Summary of the Invention

It has now been found that higher concentrations of oak bark extract possess highly useful properties for the treatment of skin cancers, and that lower concentrations of oak bark extract possess additional therapeutic properties not heretofore recognized. For example, preparations containing 40-80% oak bark extract are useful in the treatment of acute cancerous skin ulcers. In addition, it has now been found that synthetic mixtures containing potassium ions, zinc ions, calcium ions provide many of the same

advantageous properties of oak bark extract. The inclusion of rubidium ions and sulfate ions is also advantageous for some applications.

5 Detailed Description of the Invention

Oak bark extract for use in the present invention is prepared from oak bark ash. The bark utilized can be from Red Oak (Quercus rupra L), Black Oak (Quercus velutina Lam.), Shumerd Oak (Quercus shumardi i
10 Buckl.), Scarlet Oak (Quercus coccinea Muenchb.), Willow Oak (Quercus phellos L.) and other species of the Erythrobalanus group. The oak bark is burned to convert it into an ash, which is cooled and screened to provide a powder.

15 The ash powder is then poured slowly into boiling water and boiled, with stirring, for a period of time (1.5 to 4 hours) to achieve an intermediate oak bark extract. The hot intermediate extract is then filtered to recover a clear filtrate and boiled for an addition-
20 al period of time to achieve the desired final concentration of oak bark extract. During this boiling step, a white precipitate forms which is separated from the oak bark extract and discarded. Table 1 shows processing conditions which can be used to prepare oak bark
25 extract of various final concentrations. The solution concentrations are expressed as weight percent of oak bark ash derived material.

Table I

Solution (%)	Temperature (°C)	Processing Time (Hours)
0.25	98±2	1.00
1.00	98±2	2.00
10.00	98±2	8.00
20.50	98±2	12.00
40.00	98±2	18.00
80.00	98±2	21.00

The oak bark extracts in accordance with the invention are complex mixtures of inorganic materials. Further, as is evident from the results of elemental analysis on the various solutions, (See Table 2) the relative amounts of the constituents vary from one concentration to another. For example, the 40% solutions (i.e., a solutions containing a total of 40% by weight of extracted oak bark materials and 60% by weight water) was found to be highly enriched in rubidium relative to lower concentration solutions.

The therapeutic activity of various constituents of oak bark extract has been analyzed with the result that silicon, strontium, barium, manganese, gallium, zirconium and titanium appear to be unnecessary, while therapeutic efficacy has been found for compositions containing just potassium, zinc and calcium ions, in combination with suitable counterions. Thus, synthetic formulations containing, by weight of inorganic solids, 10 to 80 parts potassium ions, preferably 30 to 50 parts 0.00001 to 20 parts zinc ions, preferably 1 to 10 parts 0.01 to 10 parts calcium ions, preferably 1 to 5 parts 0 to 40 parts rubidium ions, preferably 1 to 30 parts, and 0 to 5 parts sulfur, in the form of elemen-

tal sulfur or sulfate, together with pharmaceutically acceptable counterions (e.g., Cl^- , $\text{SO}_4^{=}$, $\text{CO}_3^{=}$, OH^- , Br^-). The solution may also contain other inorganic cations, for example, up to 10 parts by weight of inorganic solids of cobalt, copper, iron, manganese, nickel, strontium or aluminum ions, preferably up to 1 part by weight. Further, the composition may include a pharmaceutically acceptable carrier such a water or an ointment or cream base which will result in a therapeutic composition having a pH of from 4 to 7, preferably pH 4.5 to 5.5.

Oak bark extract or the synthetic mixtures of the invention have been found to provide a variety of beneficial therapeutic properties. The therapeutic applications and the concentration of oak bark extract or synthetic mixture by weight of solids are summarized in Table 3.

In particular, compositions containing about 20% or more, preferably 30% to 80% and more preferably 40% to 80%, of oak bark extract or a similarly concentrated synthetic mixture according to the invention can be used to treat cancerous and precancerous skin lesions. As used herein, the term cancerous and precancerous skin lesions includes but is not limited to basal cell epithelioma, squamous cell carcinoma, keratoacanthoma.

Compositions according to the invention are also useful for treating abrasions and other partial thickness wounds. Useful compositions include at least potassium, zinc and calcium ions and may include other ionic components as well as described in Examples 1 and 2. The composition is advantageously applied in a cream or ointment base over a period of several days. Similar compositions were found to be useful in the treatment of gangrene, impetigo, psoriasis, although longer periods of treatment may be required.

TABLE 2

CONCENTRATION OF OAK BARK EXTRACT					
Element	0.25%	1.00%	10.00%	20.50%	40.00%
Hydrogen	13.77%	12.07	12.15%	11.00%	10.11%
Oxygen	86.22%	87.91	85.55%	84.40%	64.45%
Potassium	43541 ppm	0.01%	2.10%	4.50%	25.15%
Bromine	0.05 ppm	0.07 ppm	2.00 ppm	2.02 ppm	2.02 ppm
Calcium	13.43 ppm	35.67 ppm	99.45 ppm	208.72 ppm	1000.43 ppm
Chlorine	24.87 ppm	45.11 ppm	92.50 ppm	185.31 ppm	235.2 ppm
Chromium	0.23 ppm	0.55 ppm	1.01 ppm	0.49 ppm	1000.12 ppm
Cobalt	ND	ND	0.08 ppm	0.16 ppm	0.29 ppm
Copper	ND	ND	0.11 ppm	0.33 ppm	0.68 ppm
Iron	ND	ND	0.85 ppm	1.70 ppm	2.12 ppm
Lead	ND	ND	0.23 ppm	0.56 ppm	0.3 ppm
Manganese	ND	ND	0.04 ppm	0.07 ppm	0.07 ppm
Nickel	ND	ND	0.33 ppm	0.66 ppm	2.11 ppm
Rubidium	17.25 ppm	42.79 ppm	110.13 ppm	220.60 ppm	1320.23 ppm
Strontium	ND	0.01 ppm	1.79 ppm	2.99 ppm	3.3 ppm
Sulfur	5.45 ppm	30.01 ppm	180.01 ppm	373.40 ppm	421.3 ppm
Titanium	0.81 ppm	0.24 ppm	1.79 ppm	3.44 ppm	0.1 ppm
Zinc	1.74 ppm	4.78 ppm	8.81 ppm	17.65 ppm	12.3 ppm

ND: not detectable.

Table III

Weight % of Oak Bark Extract	Indications
0.25%	Fungal infection, minor infection, insect bites
1.00%	Eczema, minor burns, sunburn, poison oak, poison ivy, poison sumac, wound healing
3.00%	Pyodermas, dermatitis, pruritic dermatoses, eczema, minor burns, sunburn, poison oak, poison ivy, poison sumac, decubitus ulcers, tropical ulcers, wound healing
5.00%	Decubitus, psoriasis
10.00%	Psoriasis, impetigo, Kaposi sarcoma, warts, gangrene, ischemic ulcer, keratosis
20.50%	Precancerous lesions, basal cell epithelioma, squamous cell carcinoma, keratoacanthoma
40.00%	Acute cancerous ulcers
80.00%	Acute cancerous ulcers

While not intending to be bound by any particular mechanism of action, it appears that oak bark extract and synthetic mixtures containing the key ingredients of oak bark extract function to enhance wound healing

5 by providing complexing ions which interact with enzymes such as alkaline phosphatase, carbonic anhydrase, carboxypeptidase, various enhydrogenases, arginase, carnosinase, dehydropeptidase, glycine dipeptidase, histidine deaminase and tripeptidase,

10 oxyloacetic carboxylase, and some lecithinases and enolases. These enzymes are involved in numerous

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biosynthetic pathways necessary for wound healing, for example, collagen biosynthesis, and are believed to function with greater efficiency in the presence of the complexing ions.

- 5 The application will now be further described by way of the following, non-limiting examples.

Example 1

10 A synthetic mixture was prepared by combining potassium sulfate (7.50 g), potassium hydroxide (7.65 g), calcium hydroxide (0.05 g), iron sulfate (0.4 mg), cobaltous bromide (0.1 mg), copper chloride (0.3 mg), zinc sulfate (1.2 mg), strontium chloride (0.3 mg) and rubidium sulfate (0.13 mg) in distilled water (59.09 g)
15 and Whitfield's ointment (433.57 g). The total amount of synthetic chemicals was 3% in weight. The ointment was applied twice daily to three patients with severe abrasion. Prior to treatment, abrasions were cleaned with rubbing alcohol. All patients showed
20 disappearance of abrasion within five days of treatments.

Example 2

25 A synthetic mixture was prepared by combining zinc oxide (2.5 g), calcium hydroxide (2 g), potassium carbonate (3.5 g) and potassium hydroxide (12 g) in distilled water (80 g) and Whitfield's ointment (57 g). The total amount of synthetic chemicals was 3% in weight. This formulation was used to treat an
30 outpatient with a severe abrasion on his left arm. The abrasion was cleaned with rubbing alcohol to remove any contamination. The ointment was applied to abrasion twice daily. The abrasion healed within 72 hours.

Example 3

A synthetic mixture was prepared by combining zinc sulfate (2.5 g), calcium hydroxide (2 g), potassium carbonate (3.5 g) and potassium hydroxide (12 g) in distilled water (80 g) and Whitfield's ointment (57 g). The total amount of synthetic chemicals was 3% in weight. This formulation was used to treat an outpatient with venous stasis. The venous stasis was cleaned with a 3% solution of hydrogen peroxide, and pad dried. The ointment was applied to venous stasis twice daily. Reduction in ulcer size 60-70% within 72 hours was observed. Complete granulation within 5 days for ulcers less than 2 cm; 7 days for ulcers less than 4 cm.

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Example 4

A synthetic mixture was prepared by combining zinc sulfate (2.5 g), calcium hydroxide (2 g), potassium carbonate (3.5 g) and rubidium hydroxide (6 g), potassium hydroxide (6 g) in distilled water (80 g) and Whitfield's ointment (57 g). The total amount of synthetic chemicals was 3% in weight. This formulation was used to treat an outpatient with laceration. The laceration was cleaned with rubbing alcohol and air dried. The ointment was applied to the laceration twice daily. The laceration reduced its redness with 4 hours and healed with 72 hours.

25

Example 5

A synthetic mixture was prepared by combining potassium hydroxide (6.6 g), rubidium hydroxide (0.4 g), zinc sulfate (0.6 g), sulfur (2 g) and calcium hydroxide (0.1 g) in distilled water (14.55 g) and Whitfield's ointment (72.75 g). The total amount of synthetic chemicals was 10% in weight. This formulation was used to treat an outpatient with

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psoriasis in the right arm and right leg. The psoriasis was cleaned with rubbing alcohol to remove any contamination. The ointment was applied to abrasion twice daily. The psoriasis healed in six weeks.

Example 6

A synthetic mixture was prepared by combining potassium hydroxide (6.6 g), rubidium hydroxide (0.4 g), zinc sulfate (0.6 g), sulfur (2 g) and calcium hydroxide (0.1 g) in distilled water (14.55 g) and Whitfield's ointment (72.75 g). The total amount of synthetic chemicals was 10% in weight. This formulation was used to treat an outpatient with impetigo at the back. The back was thoroughly cleaned with rubbing alcohol to remove any contamination. The ointment was applied to impetigo twice daily. The impetigo healed in four weeks.

Example 7

A synthetic mixture was prepared by combining potassium hydroxide (6.6 g), rubidium hydroxide (0.4 g), zinc sulfate (0.6 g), sulfur (2 g) and calcium hydroxide (0.1 g) in distilled water (14.55 g) and Whitfield's ointment (72.75 g). The total amount of synthetic chemicals was 10% in weight. This formulation was used to treat an outpatient with gangrene in his feet. The gangrene was thoroughly cleaned with hydrogen peroxide to remove any contamination. The ointment was applied to gangrene twice daily. The gangrene healed in six weeks.

Example 8

A polyethylene-glycol based ointment (105 g) with 10% oak bark extract was prepared from red oak bark extract (20.5%, 100 g) to treat pustules on a patient's

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face and neck. The pustules were cleaned with a 3% saline solution. The ointment was then applied to the pustules. After 12 hours of treatment, the "angry red" face began to fade; after 20 hours, the face began to turn normal. The pustules never re-occurred.

Example 9

An aqueous solution containing 80% red oak bark by weight was prepared in accordance with the conditions outlined in Table 1. The solution was used to treat a patient with melanoma in the front of his left ear. The size of the tumor was as big as a thumbnail. At the top of it was a crusty brown. The therapy included removal of the exudate by washing the lesions with soap and water and pad dried. The solution was applied twice daily to the melanoma. After two weeks of treatments, the tumor started to clear up; and after an additional two weeks of treatments, the melanoma completely disappeared, leaving only a clean, white-looking spot.

Example 10

A polyethylene glycol-based ointment (33.33 g) with 30% oak bark extract was prepared from red oak bark extract (40.0%, 100 g) to treat venous stasis of a woman. The venous stasis was cleaned with rubbing alcohol. Air dried. The ointment was applied twice daily over a period of four days, the swelling reduced and the pain subsided.

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Example 11

Two ointments with a concentration of 20% and 50% oak bark extract solution, respectively, were prepared by mixing the 80% red oak extract solution with salicylic acid, benzoic acid and polyethylene glycol. The 20% ointment contained 100 g red oak extract

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solution (80%), 103.20 g PEG3350, 156.03 g PEG400, 30.57 g benzoic acid and 10.20 g salicylic acid. The 50% ointment contained 100 g red oak extract solution (80%), 20.64 g PEG3350, 31.21 g PEG400, 6.11 g benzoic acid and 2.04 g salicylic acid. The 50% ointment was applied twice daily to a patient with Kaposi's sarcoma. Prior to application, open lesions were cleaned with 3% hydrogen peroxide. A wet dressing was used. The size of the sarcoma reduced to a diameter of an inch after one week of treatment. The 20% ointment was applied thereafter. The patient completely healed in 45 days of treatments.

Example 12

15 An ointment with 3% oak bark extract was prepared by mixing 20.5% oak bark extract solution with salicylic acid (19.82 g), benzoic acid (59.41 g), PEG3350 (200.55 g) and PEG400 (303.22 g). The ointment was used to treat molds of a HIV-positive patient. 20 Ointment was applied twice daily to molds directly. Within 3½ weeks, molds disappeared.

Example 13

25 An ointment with 3% oak bark extract by weight was prepared by mixing 20.5% oak bark extract solution with salicylic acid (19.82 g), benzoic acid (59.41 g), PEG3350 (200.55 g) and PEG400 (303.22 g). The ointment was used to treat molds of a HIV-positive patient. Ointment was applied twice daily to molds which were 30 surgically clipped. The molds dried up within 48 hours.

Example 14

35 A male with six Kaposi's lesions was treated with an ointment containing 100 g 8% oak bark extract solution and 156.25 g polyethylene glycol. Ointment

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was applied twice daily directly over lesions. Lesions with sizes larger than one inch reduced their sizes 60% after 36 days of treatments. Lesions with sizes less than one-half of an inch healed within a week of
5 treatment.

Example 15

A polyethylene glycol-based ointment (105 g) contained 10% oak bark extract by weight, prepared from
10 100 g of 20.5% red oak bark solution, was used to treat a patient suffering from actinic keratosis. The ointment was applied twice daily over a period of four months, by which time the lesions had disappeared.

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Example 16

Five additional synthetic compositions were prepared as follows:

(a) Potassium carbonate (10g), rubidium hydroxide (4g), zinc sulfate (2.5g), calcium hydroxide (3.5g),
20 distilled water (80g), Whitfield's ointment (57g).

(b) Potassium hydroxide (10g), rubidium hydroxide (4g), zinc sulfate (2.5g), calcium hydroxide (3.5g), distilled water (80g), Whitfield's ointment (57g).

(c) Potassium carbonate (12g), rubidium hydroxide (5.5g), zinc oxide (2.5g), distilled water (80g),
25 distilled water (80g), Whitfield's ointment (57g).

(d) Potassium carbonate (12g), rubidium hydroxide (5.5g), zinc sulfate (2.5g) distilled water (80g), Whitfield's ointment (57g).

30 (e) Calcium hydroxide (12g), rubidium hydroxide (5.5g), zinc sulfate (2.5g), distilled water (80g), Whitfield's ointment (57g).

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Claim

- 1 1. A composition comprising from 40 to 80% by weight
2 of solids of an aqueous extract of oak bark.

- 1 2. A composition comprising
2 10 to 80 parts potassium ions
3 0.00001 to 20 parts zinc ions
4 0.01 to 10 parts calcium ions
5 0 to 40 parts rubidium ions, and
6 0 to 5 parts sulfur, in the form of
7 elemental sulfur or sulfate by weight of inorganic
8 solids, optionally diluted in a pharmaceutically
9 acceptable carrier, with the proviso that the
10 composition is not identical to an aqueous extract
11 of oak bark ash.

- 1 3. A composition according to claim 2, herein the
2 carrier is water.

- 1 4. A composition according to claim 2, wherein the
2 carrier is a creme base.

- 1 5. A method for treating cancerous and precancerous
2 skin lesions comprising applying to the lesion an
3 effective amount of a therapeutic composition

4 comprising therapeutically effective amounts of
5 potassium ions, calcium ions and zinc ions.

1 6. A method according to claim 5, wherein the
2 therapeutic composition is an aqueous extract of
3 oak bark.

1 7. A method according to claim 6, wherein the
2 therapeutic composition contains at least 20% by
3 weight of solids of oak bark extract.

1 8. A method according to claim 6, wherein the
2 therapeutic composition contains at least 40% by
3 weight of solids of oak bark extract.

1 9. A method according to claim 5, wherein the
2 therapeutic composition comprises
3 10 to 80 parts potassium ions
4 0.00001 to 20 parts zinc ions
5 0.01 to 10 parts calcium ions
6 0 to 40 parts rubidium ions, and
7 0 to 5 parts sulfur, in the form of
8 elemental sulfur or sulfate by weight of inorganic
9 solids, optionally diluted in a carrier.

1 10. A method for treating psoriasis comprising
2 topically applying a composition comprising an

3 effective amount of a therapeutic composition
4 comprising therapeutically effective amounts of
5 potassium ions, calcium ions and zinc ions to
6 psoriatic skin.

1 11. A method according to claim 10, wherein the
2 therapeutic composition comprises an aqueous
3 extract of oak bark.

1 12. A method according to claim 11, wherein the
2 therapeutic composition contains at least 10% oak
3 bark extract solids by weight.

1 13. A method according to claim 10, wherein the
2 therapeutic composition comprises
3 10 to 80 parts potassium ions
4 .00001 to 20 parts zinc ions
5 .01 to 10 parts calcium ions
6 0 to 40 parts rubidium ions, and
7 0 to 5 parts sulfur, in the form of
8 elemental sulfur or sulfate by weight of inorganic
9 solids, optionally diluted in a carrier.

1 14. A method for treating impetigo comprising
2 topically applying a composition comprising an
3 effective amount of a therapeutic composition
4 comprising therapeutically effective amounts of

5 potassium ions, zinc ions and calcium ions to
6 impetigos skin.

1 15. A method according to claim 14, wherein the
2 therapeutic composition comprises an aqueous
3 extract of oak bark.

1 16. A method according to claim 15, wherein the
2 therapeutic composition contains at least 10% oak
3 bark extract solids by weight.

1 17. A method according to claim 10, wherein the
2 therapeutic composition comprises
3 10 to 80 parts potassium ions
4 .00001 to 20 parts zinc ions
5 .01 to 10 parts calcium ions
6 0 to 40 parts rubidium ions, and
7 0 to 5 parts sulfur, in the form of
8 elemental sulfur or sulfate by weight of inorganic
9 solids, optionally diluted in a carrier.

1 18. A method for treating gangrene comprising
2 topically applying a composition comprising an
3 effective amount of a therapeutic composition
4 comprising therapeutically effective amounts of
5 potassium ions, calcium ions and zinc ions to
6 gangrenous tissue.

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- 1 19. A method according to claim 19, wherein the
2 therapeutic composition comprises an aqueous
3 extract of oak bark.
- 1 20. A method according to claim 18, wherein the
2 therapeutic composition contains at least 10% oak
3 bark extract solids by weight.
- 1 21. A method according to claim 18, wherein the
2 therapeutic composition comprises
3 10 to 80 parts potassium ions
4 .00001 to 20 parts zinc ions
5 .01 to 10 parts calcium ions
6 0 to 40 parts rubidium ions, and
7 0 to 5 parts sulfur, in the form of
8 elemental sulfur or sulfate by weight of inorganic
9 solids, optionally diluted in a carrier.